## REMARKS

Upon entry of this amendment, Claims 1, 3-5, 14-34, and 37-41 constitute the pending claims in the present application. Among them, Claims 3, 28, and 29 are directed to non-elected species, and are withdrawn from further consideration.

Claims 35 and 36 are canceled without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope to all the canceled claims in future continuing application(s).

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

*Claim Rejections under 35 U.S.C. § 112, second paragraph*

The Office Action rejects Claim 16 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Office Action alleges that the term "potency" makes claims confusing, and requires Applicants to change it to the "commonly known term in (the) art" (emphasis original) such as "enzyme activity."

While Applicants do not necessarily agree with the Examiner's arguments, solely to advance prosecution, Applicants have amend Claim 16 to replace "potent" with "active." Applicants submit that the amendment does not change the scope of the claims.

Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

*Claim Rejections under 35 U.S.C. § 112, first paragraph*

Claims 35, 36, and 38-40 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement.

Regarding Claims 35 and 36, the Office Action asserts that Claims 35 and 36 "broadly recite the use of **any** substrate polypeptide, which is cleaved by adzyme to produce any product that inhibits the substrate binding or adzyme cleavage," while the specification "fails to describe

how any cleavage-product of any substrate polypeptide inhibits the substrate or the proteolytic cleavage of adzyme ...."

Applicants again respectfully disagree with the Examiner's reasoning. Nevertheless, solely to advance prosecution, Applicants have canceled Claims 35 and 36 to obviate this rejection.

Claims 38-40 are rejected under 35 U.S.C. § 112, 1st paragraph, for allegedly failing to meet the enablement requirement. The Office Action asserts that these claims "recite an adzyme composition formulated in any way to present [sic] autocatalytic proteolysis (38) or specifically a reverse inhibitor is added (39-40). However reversible inhibitors are not likely available for many protease and other means of formulating to inhibit autocatalysis are not taught." In other words, the Examiner argues that the specification has not taught one of skill in the art how to make the claimed invention in Claims 38-40.

Applicants respectfully disagree. Applicants have previously argued that there are numerous art-recognized reversible protease inhibitors, many (if not all) are commercially available. For example, **Sigma-Aldrich** sells numerous **broad-spectrum protease inhibitors**, such as Serine protease inhibitors, Cysteine protease inhibitors, Aspartic protease inhibitors, and Metalloproteinase inhibitors, including Leupeptin, Aprotinin, Pepstatin A, EDTA, *etc.* *See* http://www.sigmaaldrich.com/Area_of_Interest/Biochemicals/Enzyme_Explorer /Key_Resources/Protease_Inhibitors/Broad_Spectrum_Inhib_.html (**Exhibit A**).

Also *see* the **Santa Cruz Biotechnology, Inc.** web site http://www.scbt.com/support-table-protease_inhibitors.html, and **CALBIOCHEM** web site for properties of selected protease inhibitors www.emdbiosciences.com/html/cbc/Protease_Inhibitor_Properties.htm (**Exhibit A**).

According to these companies, **Leupeptin** reversibly inhibits trypsin-like serine proteases such as trypsin, chymotrypsin, chymase, pepsin and thrombin, it also inhibits selected cysteine proteases such as calpain, cathepsin B, H & L and papain; **Aprotinin** is a reversible inhibitor of esterase and serine protease activity such as trypsin, chymotrypsin, kallikrein, plasmin, urokinase, and leukocyte protease; **Pepstatin A** is a reversible inhibitor of acid proteases such as pepsin, renin, chymosin, protease B and cathespin D and many microbial aspartic proteases;

**EDTA** is a reversible metalloprotease inhibitor. *See* **Exhibit A.**

The Examiner argues that "reversible inhibitors are not likely available for many proteases," which seems to be contradictory to the evidence Applicants have provided. On the other hand, the Examiner has not provided any scientific reasoning or evidence to support his assertion. If this assertion is based on personal knowledge, Applicants respectfully invite the Examiner to provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. *See* 37 C.F.R. § 1.104(d)(2). Applicants also respectfully remind the Examiner that "[i]f applicant adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. *See* 37 CFR 1.104(c)(2). *See* also *Zurko*, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test)." *See* MPEP 2144.03, Section C.

In that regard, Applicants also respectfully remind the Examiner that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987)." MPEP 2164.01(b).

Therefore, based on the teaching of the instant specification, coupled with what is well-known in the art, a person of ordinary skill in the art would be able to formulate the claimed pharmaceutical preparation to prevent autocatalysis, for example, by using a myriad of available reversible protease inhibitors, such as those described herein.

In view of the foregoing, all pending claims satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

*Claim Rejections under 35 U.S.C. § 102*

The Office Action rejects Claims 1, 4, 14, 16-25, 30-41 under 35 U.S.C. § 102 as allegedly being anticipated by Davis *et al.* (WO 00/64485, "Davis") or Chen *et al.* (US 2003/0068792, or "Chen").

In response to Applicants' previous argument that Davis, or Chen does not teach a fusion protein resistant to autoproteolytic cleavage, the Office Action maintains the rejection by continuingly relying on a wrong interpretation of the term "fusion protein."

Applicants hereby reiterate that the neither Chen nor David teaches a "fusion protein" recited in the claims.

Specifically, Chen relates to a so-called "targeted enzyme" that "comprises a substrate recognition site and has been modified from a pre-targeted enzyme to comprise one or more targeting sites, each targeting site comprising one or more variant sequences, and to bind to a target with higher affinity than the corresponding pre-targeted enzyme binds the target under like conditions. ... Targeted enzymes of the invention **do not include** enzymes with a targeting site that consists of a polypeptide or other target-binding molecule that is attached to the N- or C-terminus of the pre-targeted enzyme (e.g., as in a histidine tagged protein or **a fusion protein**), a targeted enzyme whose only target is a monoclonal antibody, or a targeted enzyme made by increasing or optimizing the binding of a pre-targeted enzyme to a substrate of a reaction catalyzed by the pre-targeted enzyme" (emphasis added).

In other words, the "targeted enzyme" of Chen merely modifies so-called "variant sequences" on the pre-targeted enzyme, such that after the modification, the enzyme acquires the ability to bind a target that the enzyme previously cannot bind. In doing so, Chen explicitly states that the "targeted enzyme" **does not include** any fusion protein created by fusing a targeting domain to (the catalytic domain of) a discrete and heterologous enzyme (see emphasis above), as is recited in the claimed invention.

The above disclosure in Chen, especially the bold emphasis "targeted enzymes of the invention **do not include** ... **a fusion protein**," is directly contradictory to the Examiner's assertion that "Chen et al teach a fusion protein ..." Applicants reiterate that the targeted enzyme

in Chen is not a fusion protein with a catalytic domain fused to a "heterologous" targeting domain, because what Chen calls "catalytic polypeptide domain" and "targeting site" are from the same "pre-targeted enzyme" (see quoted passage above).

If the Examiner wishes to maintain this rejection, Applicants respectfully invite the Examiner to explain for the record why and how the Chen construct can be viewed as a "fusion protein" with "discrete and heterologous" "catalytic polypeptide domain" and "targeting site," as recited in the claims, despite the fact that Chen explicitly denies that its construct is such a fusion protein.

Likewise, although the Examiner has admitted that "David et al. fuse a catalytic domain (like protease) to a targeting moiety via chemical cross linking agent" (emphasis added, see page 7, towards the end of the first paragraph in the July 25, 2007 Office Action), the Examiner has apparently misunderstood the meaning of "fusion protein" as recited in the claims. According to the Examiner's interpretation, two or more chemically cross-linked polypeptides (such as those taught in Davis) are also "fusion proteins."

Applicants reiterate that chemically cross-linked two or more polypeptides are not a single "fusion protein" within the scope of the claims.

In summary, Applicants submit that neither Chen nor Davis teaches a "fusion protein" as recited in the claimed invention, and thus neither can anticipate the claimed invention. Reconsideration and withdrawal of the rejections are respectfully requested.

*Claim Rejections under 35 U.S.C. § 103*

The Office Action rejects Claims 1, 4, 14-17, 18-27, 30-38, and 41 under 35 U.S.C. § 103(a) as allegedly being obvious in view of Davis (*supra*) or Chen (*supra*) or Guo *et al.* (*Biotec. and Biong* **70**: 456-463, 2000, or "Guo") in view of Sallberg *et al.* (U.S. Pat. No. 6,960,569) or Whitcomb (*supra*).

Specifically, the Examiner argues that, although Davis and Chen do not teach adzymes with protease domains resistant to auto-cleavage, Whitcomb teaches mesotrypsin, which is resistant to PSTI inhibition; and Sallberg teaches "fusion protein of mutated NS3/4A protease

domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolytic cleavage)."

Thus, the Examiner concludes that "... it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is resistant to trypsin inhibitor as taught by Whitcomb et al. or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo *et al.* to target domain as thought [sic] by Davis ... or Chen and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of [sic] the said substrate polypeptide."

Applicants respectfully disagree for the reasons which follow.

First of all, Applicants submit that **there is no motivation to combine Davis or Chen with Guo, Whitcomb, or Sallberg** to arrive at a fusion protein having a protease domain resistant to auto-cleavage.

As argued before (see above), neither Chen nor Davis teaches or suggests a fusion protein that is resistant to auto-cleavage as recited in the claims. Applicants submit that Whitcomb, Sallberg, and Guo do not make up this deficiency.

Specifically, regarding fusion protein, Applicants submit that, because both Chen and Davis explicitly teaches away from using "fusion proteins," Guo, Whitcomb, and Sallberg cannot be properly combined with Chen or Davis, because doing so would change the principle of operation in Chen and Davis.

Pursuant to MPEP 2143.01: "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (C.C.P.A., 1959)." Therefore, neither Chen nor Davis can be combined with Guo.

Furthermore, regarding resistant to auto-cleavage, the Examiner does not argue that Guo contains any disclosure that makes up the deficiency in Davis or Chen concerning resistant to auto-cleavage. Neither has the Examiner argued or explained why the combination of Whitcomb

with Davis or Chen teaches an adzyme resistant to auto-cleavage, since Whitcomb apparently teaches that mesotrypsin is resistant to inhibition by a protease inhibitor such as PSTI, which is largely irrelevant to resistant to auto-cleavage. Apparently, there is nothing in Whitcomb that teaches or suggests that mesotrypsin is also resistant to auto-cleavage. It is unclear why one of skill in the art would have been motivated to combine Whitcomb with either Chen or Davis in view of this apparently irrelevant disclosure in Whitcomb.

Applicants further submit that one of skill in the art would have had no motivation to combine Sallberg, because Sallberg does not teach or suggest an **NS3 protease domain that is resistant to auto-cleavage**. In fact, The Examiner has not provided any reason in the last Office Action as to why one of skill in the art would have been motivated to combine Sallberg. Applicants have previously requested the Examiner to provide at least one reason for the motivation to combine. However, the Office Action still has not offered *any* reason as to the motivation to combine Sallberg, which is required for establishing a *prima facie* case of obviousness.

If the Examiner is relying on the proposition that Sallberg teaches a protease-antibody conjugate with a protease domain resistant to auto-cleavage, Applicants submit that this understanding is wrong for the reasons of record (see Applicants' previous Office Action response filed on May 22, 2007). The Examiner has not rebutted Applicants argument in this Office Action.

Applicants submit that there is not any disclosure in Sallberg that relates to conjugating the NS3/4A fusion protein to antibody or other protein, as the Office Action alleges. Sallberg relates to the identification of a new NS3/4A fusion of the HCV virus, its truncation mutants, or its mutations that lack a proteolytic cleavage site. *See* col. 3, lines 30-50. Sallberg contemplates the use of such HCV peptides as immunogens to generate antibodies against NS3 (*see* col. 3, last paragraph). **Applicants, however, were unable to find any disclosure about any conjugates of such NS3/4A fusion to any antibodies or other proteins**. If the Examiner wishes to maintain this rejection, Applicants respectfully invite the Examiner to point out the specific page and line numbers in Sallberg that allegedly teach the "NS3/4A-antibody fusion."

Although Sallberg may have disclosed a proteolytic resistant mutant of the NS3/4A fusion protein, **it is unclear whether the mutation occurs within the NS3 Ser protease domain or elsewhere in the NS3/4A fusion**. In fact, the mutation most likely does not occur within the NS3 protease domain, since the protease resistant site is between the NS3 and NS4A fusion parts (see Example 3 (col. 14)).

Furthermore, Sallberg **teaches away from using the protease resistant protein**. In Example 3, it is shown that, while the protease resistant version of the NS3/4A mutant is still "comparable" to the wild-type NS3 protein in terms of immunogenicity, the NS3/4A fusion that is not protease resistant works better as an immunogen than the protease resistant version. "...the NS4A sequence and a functional proteolytic cleavage site between the NS3 and NS4A sequences provided for a more potent immune response" (emphasis added). *See* col. 3, Example 3 and Table 2.

Secondly, Applicants submit that even if one of skill in the art is motivated to combine Whitcomb or Sallberg with Davis or Chen, **the combined teaching still fails to teach or suggest all the limitations of the claimed invention**.

As argued above, Whitcomb apparently teaches that mesotrypsin is resistant to inhibition by a protease inhibitor such as PSTI, which is largely irrelevant to resistant to auto-cleavage. Apparently, there is nothing in Whitcomb that teaches or suggests that mesotrypsin is also resistant to auto-cleavage. Thus a combination of Whitcomb with Davis or Chen still does not teach or suggest the resistant to auto-cleavage limitation in the claims.

Also as argued above, because Sallberg fails to teach **any protease-resistant version of the NS3 protease**, even if it is combined with the other cited references, the combined teaching still would have failed to teach or suggest all the limitations of the claimed invention.

In summary, other than mere conclusory statements, the Office Action has failed to identify any reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. In addition, even assuming for the sake of argument that

Whitcomb or Sallberg can be combined with Davis or Chen, the combined teaching still fails to teach or suggest all the limitations of the claims in each case. Therefore, a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.

*Double Patenting Rejection*

The Office Action states that Claims 1, 4-25, and 30-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1, 4-25, and 30-41 of the co-pending U.S. Application No. 10/792,498.

The Office Action also states that Claims 1, 4-25, and 28-41 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1, 4-38, 40-46, 52-60, 66-104, 107-134 of the co-pending U.S. Application No. 10/650,592.

Applicants submit that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

Applicants note that no claim has been issued in the co-pending application Nos. 10/792,498 and 10/650,592. Thus if the only rejection in the instant application is the provisional double patenting rejection, the Examiner should withdraw that rejection and permit the application to issue as a patent without requiring a terminal disclaimer.

If conflicting claims are first allowed in the co-pending U.S. Application No. 10/792,498 or U.S. Application No. 10/650,592, and appear in an issued U.S. patent, Applicants note that, pursuant to 37 C.F.R. § 1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

## CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P02-001**.

Dated: October 25, 2007

Respectfully submitted,

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